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THE RESISTANCE OF FIXED TISSUE CELLS TO THE TOXIC ACTION OF CERTAIN CHEMICAL SUBSTANCES[1]

By Professor WM. deB. MacNIDER

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ANY consideration of the general question of tissue resistance has of necessity to first take into account the two monuments in this division of understanding and later the particulate research which these initial contributions stimulated. First, the biological conception of Metchnikoff[2] of the protection and the resistance afforded tissues through the activity of wandering cells, and second, the chemical or humoral theory of Ehrlich[3] which postulated the production on the part of tissues reacting to injurious agents of substances highly specific in nature which had the ability to bind or destroy those agents which had incited their formation. The fundamental work of Metchnikoff has been amplified and made specific through investigations of a major character by Aschoff,[4] Mallory,[5] Maximow,[6] Sabin,[7] Gay,[8] Cunningham[9] and their pupils so that at the present time the wandering phagocytic cells of the

[1] This investigation was made possible through a grant from The Josiah Macy, Jr., Foundation. Address delivered before the General Session of The Federation of American Societies for Experimental Biology; Detroit, April 13, 1935.

[2] Metchnikoff, "L'immunitié dans les maladies infectieuses." Mason et Cie., Paris, 1901.

[3] Ehrlich, *Deut. Med. Wchnschr.*, 17: 976, 1891.

[4] Aschoff, *Ergeb. inn. Med. u. Kinderh.*, 26: 1, 1924.

[5] Mallory, *Jour. Exp. Med.*, 3: 611, 1908.

[6] Maximow, *Arch. Path.*, 4: 557, 1927; *Arch. exp. Zellforsch.*, 5: 169, 1928.

[7] Sabin, *Physiol. Rev.*, 2: 38, 1922.

[8] Gay, The Harvey Lectures, 1930–31, Williams and Wilkins, Baltimore.

[9] Cunningham, *Am. Jour. Physiol.*, 59: 1, 1922.

body and certain fixed phagocytic cells have become recognized as one of the most essential defense mechanisms which the organism utilizes against living agents of disease.

The humoral theory of Ehrlich, though at first standing apart from the earlier conception of Metchnikoff, has through continued investigation not only established itself as an entity in a chemical sense, but such studies indicate the origin of many of these bodies of a specific chemical character to be intimately associated with the specific activity of different types of cells found in the macrophage system. More and more the conception of Ehrlich takes its place as an integral and essential part of the biological defense mechanism first postulated by Metchnikoff.

As far-reaching in their applications as these two conceptions, or a combination of the two may be, there are certain types of tissue resistance which they fail to explain. The congenital and acquired resistance of certain tissues to chemical substances has no cytological or humoral explanation: the congenital tolerance of the parasympathetic endings of the rabbit for atropine when such endings have a normal degree of sensitivity to other agents acting through them; the acquired tolerance of the central nervous system to the alkaloids of opium, even though this tissue, as was shown by Rubsamen,[10] may contain a very high percentage of such bodies. The development of "dye fast" and specifically "arsenic fast" protozoa,[11] especially the trypanosomes, whose resistance to such agents may be transmitted to subsequent generations of organisms,[12] furnishes a group example of acquired tissue resistance on the part of organisms for which there is no explanation.

Tissue resistance not infrequently develops as a sequence to processes of repair. Through inflammation or chemical degeneration, cells of functional value are lost and become replaced by entirely different types of cells which either have no functional value, or their type of function is so changed that they are no longer of value to the organism in a normal, functional sense. The formation of fibrous tissue secondary to tissue destruction, the encystment of parasites or foreign bodies and the localization of an inflammatory area are familiar examples of such a process. Somewhat different, but resembling this form of repair, is the shift in cell type which was observed by Wolbach,[13, 14] and Wolbach and Howe[15] in their studies of vitamin deficiency in which normal epithelium was replaced by keratinized cells. Here again tissue resistance is acquired, but it is not acquired by the formation of cells which are of functional value. Such cell resistance developing as a result of a change in cell type is dependent upon a lack of exposure of the altered cells to the injurious agent. Tissue resistance should imply the ability of cells to function to some extent in a normal manner, to subject themselves to an injurious agent and to withstand in various degrees the action of such an agent. Related to this type of resistance dependent upon injury followed by a repair process in which fixed tissue cells undergo a metaplasia, retaining in part their function and yet becoming resistant to injury, fall the experimental observations which form the basis of this communication.

In experiments[16, 17] conducted many years ago, which were primarily concerned with a study of renal regeneration subsequent to an interference with the blood supply to the kidney, the observation was made that in such areas of restricted blood supply, the epithelial regeneration which occurred was of an abnormal type. The environment created experimentally in such areas was unable to maintain the physical integrity of the highly specialized type of cell which occurs in the convoluted tubules but could maintain a flattened type of cell with less specialized cytological characteristics. There was not then, and there is not now, any way to ascertain in the higher animals the functional value of such cells exclusive of other intimately related structures, the glomeruli.

In a later study[18] of the naturally acquired chronic nephropathy of the dog this same type of cell was observed as having taken the place of cells in the convoluted tubules. When such a shift in cell type had occurred as a reaction to injury during the course of a chronic nephritis it was found that such cells originating as a repair process were resistant to uranium nitrate, while the normal type of cell in this segment of the tubule had no resistance against this nephrotoxic agent. Years later than this Gil y Gil[19] observed that the kidney of the rabbit, the seat of a chronic injury from uranium, developed a certain degree of resistance against this agent. A similar observation was also made by Hunter.[20] Recent studies[21, 22, 23] from this laboratory of the acute and

[10] Rubsamen, *Arch. f. exp. Path. u. Pharm.*, 59: 227, 1908.
[11] Voegtlin, Dyer and Miller, *Jour. Pharm. Exp. Ther.*, 25: 55, 1924.
[12] Woodruff, "Organic Adaptation to Environment," Yale University Press, New Haven, 1924.
[13] Wolbach, *Jour. Exp. Med.*, 43: 753, 1925.
[14] Wolbach, *Archiv. Path.*, 5: 239, 1928.
[15] Wolbach and Howe, *Jour. Exp. Med.*, 57: 511, 1933.
[16] MacNider, *Jour. Med. Research*, 19: 425, 1911.
[17] *Ibid.*, 20: 369, 1911.
[18] *Ibid.*, 29: 177, 1916.
[19] Gil y Gil, *Beit. z. path. Anat., u. Allg. Path.*, 72: 621, 1924.
[20] Hunter, *Ann. Int. Med.*, 1: 747, 1928.
[21] MacNider, *Jour. Exp. Med.*, 49: 411, 1929.
[22] MacNider, The Harvey Lectures, 1928–29, Williams and Wilkins Company, Baltimore; *Amer. Jour. Med. Sci.*, 178: 449, 1929.

chronic nephritis induced in the dog by uranium nitrate have not only emphasized the selective affinity which uranium has for the convoluted tubule cells and the resistance which the kidney may acquire to this toxic agent, but certain of these studies have become more specific in their understanding of the nature of this resistance in that they have shown that it is dependent upon two factors: first, the severity of the epithelial injury; and second, the type of fixed tissue cell which develops as a process of repair in such injured areas.

If a slight epithelial injury be induced in the convoluted tubule cells of a young dog by the subcutaneous use of 2 mgs of uranium nitrate per kilogram, there develops evidence of degeneration in these cells which is followed by a process of repair which results in the formation of cells normal cytologically for this segment of the tubule. When animals with this type of normal epithelial repair are subjected to a secondary intoxication by uranium, in the same amount per kilogram, they fail to show any evidence of resistance to this nephrotoxic agent. The epithelium undergoes a process of degeneration. During these experiments other animals were intoxicated by 4 and by 6 mgs of uranium nitrate per kilogram with the development of a more severe type of injury to the convoluted tubule cells. A large percentage of such animals failed to survive. In those animals effecting a survival a study of biopsy material has shown the convoluted tubule segment to be repaired by an entirely different type of epithelial cell. A cell metaplasia has developed with the formation of cells abnormal in their morphology for this portion of the tubule which are characterized by their flatness, an intensity of staining of both cytoplasm and nuclei, and a tendency to persist as syncytial structures. When such animals are reintoxicated by uranium in the amount employed for the first intoxication or to an amount not exceeding 8 mgs per kilogram, the atypical type of epithelial replacement fails to undergo changes of degeneration. As a reaction to a severe type of injury epithelial repair to the convoluted tubules has taken place by the formation of an abnormal type of epithelial cell which imparts to this segment of the tubule a high degree of resistance to the toxic action of this chemical substance. The functional value of this type of epithelial replacement can not be directly ascertained.

The question then arises, are such processes of repair which depend upon fixed cell metaplasia of such a nature that these cells having a functional value in turn subject themselves to the toxic action of this chemical and resist its toxic influence? In order to answer this question and for the purpose of ascertaining if the same factors influenced fixed cell resistance in other organs, the liver has been studied both functionally and structurally during phases of injury followed by periods of different types of cell repair.

The fact was established through the investigations of Whipple and Sperry[24] that when chloroform was given to dogs under standard conditions there occurred a central necrosis of the liver lobules involving one half to two thirds of their area. A technique similar to this has been employed to ascertain whether or not the livers of animals injured by uranium nitrate and subsequently repaired by different types of fixed cells has or has not acquired a resistance to chloroform when given by inhalation.[25] During these experiments the functional effectiveness of the liver has been ascertained by the use of phenyltetrachlorphthalein, according to the technique developed by Rosenthal.[26]

When young dogs are intoxicated by uranium nitrate given subcutaneously in the amount of 2 mgs per kilogram, there usually occurs by the third day evidence of hepatic dysfunction, which is indicated by an increase in the initial plasma concentration of this dye and by a delay in its removal from the plasma. Such a concentration has rarely gone above 13 per cent. and the delay in the removal of the dye has not been prolonged beyond an hour. At such a period of hepatic injury the epithelium has shown cloudy swelling, an increase in granulation and an abnormal accumulation of stainable lipoid material. Vacuolation and necrosis of the cells has usually been absent. The vascular tissue of the liver and the bile duct epithelium do not participate in the injury. Within eight to twenty days this degree of epithelial injury is repaired by the formation of a normal type of polyhedral epithelial cell and associated with such a repair, liver function as indicated by the use of phenoltetrachlorphthalein returns to its normal value. At such period of liver recuperation the animals were starved for twenty-four hours and anesthetized with chloroform for one and one-half hours. Such a procedure has caused the development of a central necrosis of the liver lobules, which is variable in its extent and which is associated with a depression in hepatic function. A slight liver injury induced by uranium is followed by a fixed cell repair to the liver resulting in a restoration of liver function which is dependent upon the formation of a normal type of liver epithelium. The liver, the seat of this type of repair process, has failed to acquire any resistance to chloroform. The repaired hepatic cells undergo necrosis in the same location in the lobules and

[23] MacNider, SCIENCE, 63: 103, 1931.

[24] Whipple and Sperry, *Bull. Johns Hopkins Hosp.*, 20: 278, 1909.

[25] MacNider, *Trans. Ass. Amer. Physicians*, 49: 14, 1934.

[26] Rosenthal, *Bull. Johns Hopkins Hosp.*, 33: 432, 1922.

in general to the same extent as occurs in the livers of normal dogs.

In a second series of experiments an intoxication was induced by the use of 4 mgs of uranium nitrate per kilogram. When the amount of uranium is increased to this extent a severer type of intoxication is established which may lead to the death of the animals. In those animals which have effected a survival the experiments have had the following course: As a result of the severe liver injury there occurs a higher initial plasma concentration of phenoltetrachlorphthalein which reaches its maximum between the fourth and sixth days of the injury. A concentration as high as 32 per cent. has been obtained at such a period. The dye is not removed from the plasma in a two-hour period. At such a stage of acute injury the hepatic epithelium has shown vacuolation with partial and in areas complete necrosis, a marked increase in stainable lipoid material in the better preserved cells with only a minor degree of invasion of such areas by polynuclear and monocytic cells.

The repair to the liver from an injury of this severity is completed between the fourth and the tenth week. The repair is accomplished by the formation of an atypical type of epithelium which is not patchy but is diffuse in its distribution. The cells and cell cords are flattened, leaving between them greatly enlarged hepatic sinuses. The cytoplasm of such epithelium has a dense appearance and stains intensely and evenly. The nuclei are large in proportion to the surrounding cytoplasm and appear hyperchromatic. In many of the liver cords the cells have not differentiated but remain as syncytial structures. Associated with this type of liver repair there has developed an improvement in hepatic function which in the case of a few animals has returned to the normal. There is evidence therefore that this type of epithelial cell is possessed of definite functional value.

At such periods of liver repair associated with a partial restoration in liver function, chloroform has been given by inhalation in order to ascertain whether or not this type of cell had acquired any degree of resistance against this toxic chemical agent. The animals were starved for twenty-four hours and deeply anesthetized for three hours, an hour and a half in excess of the time necessary to induce liver necrosis in normal dogs and in dogs in which a liver repair had occurred through the formation of a normal type of epithelial cell. In the group of animals now under consideration in which the liver repair had been effected through the formation of an atypical type of cell there was no histological evidence of liver injury. At the termination of the periods of anesthesia the functional effectiveness of the liver in so far as its ability to remove phenoltetrachlorphthalein was concerned was variable. In the larger number of animals at such a period the initial plasma concentration of the dye and the rate with which it was removed was greater than the concentration and rate of removal which the livers of such animals in a state of repair had established as their pathological normal. In a smaller percentage of animals the functional value of the liver was not interfered with. From these experiments it would appear that dependent upon the type of repair process provoked in the liver by the use of uranium, a resistance is acquired on the part of this organ to the toxic action of chloroform when it is given under standard conditions in an amount much in excess of that necessary to induce an injury to a normal type of liver cell.

The question then arises concerning the degree of resistance which has been acquired by this type of cell. Is the resistance complete, or is it relative to the amount of the toxic agent employed and the duration of the exposure of such resistant cells to it? The degree of resistance in this instance as is likely the case in all forms of tissue resistance is relative in its nature, as is shown by the fact that if animals which have acquired a liver resistance to chloroform when starved for twenty-four hours and given chloroform for three hours be again starved not for twenty-four but for forty-eight hours and given chloroform for four hours on one day or for three hours on two successive days, there then occurs a central injury to the liver lobules which, if sufficiently extensive, is expressed by a reduction in hepatic function.

During the thirteen years through which this general plan of investigation has been in effect, dogs have been studied which on account of their age may be classified as senile animals. Such animals have varied in age from eight to fourteen years, have shown the local manifestations of senility, are generally underweight for their variety, but without evidence of a definite process of disease. In twenty-one of ninety-two dogs which have fallen in this group, histological studies of the liver have shown the occurrence of an alteration in the structure of the hepatic epithelium similar to that which has been described as occurring in those animals which have survived a severe injury to the liver from uranium in which the liver repair was effected by the formation of an atypical type of hepatic epithelium. There occurs therefore in a certain number of animals, in a group which may be designated as senile, a change in the type of epithelial structure of the liver. When such animals are starved for twenty-four hours and given chloroform by inhalation for one and one-half hours, there fails to develop a central necrosis of the liver lobules. The removal of phenoltetrachlorphthalein from the plasma is not interfered with. If, however, the period of starvation be increased to forty-

eight hours and chloroform be given for four hours, a central injury to the liver lobule develops. These observations are of particular interest in that they show that a shift in cell type may develop in the liver without the use of an agent distinctly abnormal to this tissue, that the change may be acquired as a product of senility and that when it develops it imparts to the liver a degree of resistance to chloroform comparable to that induced by a process of repair following a severe hepatic injury from uranium nitrate.

CONCLUSIONS

(1) The observations which have been made concerning an acquired resistance of fixed tissue cells to chemical injury should be considered of a gross order and perhaps superficial in their nature. Studies of the mitochondria, the Golgi apparatus and the chemical constitution of such resistant cells afford important suggestions for investigation.

(2) The type of fixed cell response which develops in both the kidney and liver as a reaction to injury induced by uranium nitrate depends upon the severity of the injury to the epithelial structure of these organs. If the injury which is inflicted be slight as indicated by cytological changes of degeneration and in the case of the liver by but minor interference in one manifestation of its function, the process of repair results in the formation of a normal type of epithelial cell. This type of repair process is not associated with the acquisition on the part of the kidney of any degree of protection against subsequent intoxications by uranium or in the case of the liver against the toxic action of chloroform.

(3) If the injury to the epithelium of the kidney or the liver be of a sufficiently severe order, there occurs in such animals the development of a process of epithelial repair which is atypical in character and which imparts to the kidney a relative resistance against subsequent intoxications by uranium and in the liver a similar protection against the toxic action of chloroform.

(4) This protection is not dependent upon the development during the process of repair of a type of cell which is functionally inert and therefore one which does not subject itself to the action of the toxic agents. The morphologically altered hepatic epithelium maintains its functional effectiveness, as is indicated by its ability to remove phenoltetrachlorphthalein from the plasma and furthermore when such changed fixed tissue cells in the liver are subjected to the toxic action of chloroform in a concentration and for a duration far in excess of that employed under standard conditions, they show evidence of injury and liver function becomes depressed.

(5) The observation has been made of the natural occurrence in the livers of certain senile animals of a type of morphologically altered epithelium similar in its configuration and staining reactions to the cells which may develop in the liver reacting to a severe injury from uranium nitrate. Such cells impart to the livers of senile animals an acquired resistance to the toxic action of chloroform.

(6) It would appear from these experiments that a tissue resistance to certain chemical substances may depend upon the development in tissues as a process of repair following injury of an altered type of resistant fixed tissue cell which maintains a sufficient degree of functional effectiveness to enable the organism as a whole to survive.

OBITUARY

EDWIN BRANT FROST
1866–1935

EDWIN BRANT FROST was born on July 14, 1866, at the pleasant town of Brattleboro in the southeastern corner of Vermont. It was here or in the immediate neighborhood that most of his forbears for several generations had lived and flourished. The first of the name in this country was Edmund Frost, who came to Boston in 1634, his grandchildren moving west to New Hampshire and Vermont. Edwin was the second son of Carleton Pennington Frost (1830–1896), who practiced medicine in Brattleboro and neighboring towns until 1871, when he moved with his family to Hanover, New Hampshire, there to be a professor in the Dartmouth Medical School and afterwards dean of the school and a trustee of the college.

Edwin was graduated A.B. at Dartmouth in 1886. The year following he continued postgraduate work at Dartmouth, taught school in a nearby village and at the end of the year spent a few months at Princeton, where he came under the influence of Charles Augustus Young (1834–1908), then perhaps the leading teacher of astronomy in this country. An appointment to an instructorship at Dartmouth came in 1887. At that time advanced work in astronomy and in almost every other branch of science meant a year or more in Europe. Accordingly, Frost secured a two-years leave (1890–1892) to visit most of the European observatories and to spend the second year at Potsdam in Germany, where Vogel was establishing an observatory devoted especially to the new science of astrophysics and where he had gathered around him an

exceptionally brilliant staff, all of them leaders in their chosen fields: Scheiner, Müller, Kempf, Wilsing, Hartmann, Ludendorff, Eberhard, Lohse. Frost thus had an opportunity to come into contact with a group that it would have been difficult to match at a single institution either in that day or during the twenty years to follow. When he returned to Dartmouth in 1892 it was as assistant professor, and this promotion was followed in 1895 (when he was only twenty-nine years of age) by a full professorship and the directorship of the Dartmouth Observatory.

While at Potsdam Frost made arrangements with Scheiner to translate into English the latter's "Spectralanalyse der Gestirne" (1891). Frost's work appeared in 1894. It is more than a translation, for although there was only three or four years between the two books, much progress had been made in astronomical spectroscopy in the interval, and Frost brought the work up to date, besides incorporating some new matter in the form of tables. Frost's book played an important part in the rapid development of the science in this country, and until very recently it remained the standard work on the subject in our language.

The lines along which Frost's career was likely to develop must have seemed unusually clear to him at this time, and doubtless he looked forward to a long term of usefulness to his Alma Mater. But a series of apparently remote events rapidly and completely changed his outlook. James Edward Keeler (1857–1900) had left the Lick Observatory in 1892 to take charge of the Allegheny Observatory in Pittsburgh. There he at once made a striking series of spectroscopic observations with the meager equipment at his disposal. One effect of this success was to give great impetus to a movement to erect a new Allegheny Observatory, with a thirty-inch refractor as its principal instrument. When something more than half of the amount of money necessary for this project had been raised, business conditions in Pittsburgh caused the fund to halt, and Keeler had to look forward to some additional years with the old equipment. Those were the days when Catherine Bruce, of New York City, was devoting a good deal of her income to further astronomical research in all quarters of the globe. In 1897, Dr. George E. Hale, director of the recently completed Yerkes Observatory at Williams Bay, Wisconsin, successfully applied to Miss Bruce for a grant sufficient to bring Keeler to the Yerkes Observatory for five years and to set on foot an extensive program of spectroscopic observations of the stars. He was to go to the Yerkes in the summer of 1898, but in the spring of that year he received a most unexpected call to succeed Holden as director of the Lick Observatory. In common with every one else concerned he felt that he could not refuse this call. For the place thus left open at the Yerkes Observatory Dr. Hale naturally turned to Professor Frost, who took up his duties at Williams Bay in the summer of 1898, expecting to stay for five years only. But before the end of this term the outlook had again changed, for Hale had been organizing what was at first an expedition from the Yerkes Observatory to California to observe the sun under more favorable climatic conditions. As every one knows, this expedition grew into the Mount Wilson Observatory. In the two years following 1903 much of the responsibility for the conduct of the Yerkes Observatory fell to Frost. On Hale's resignation as director in 1905, Frost was appointed to succeed him in June of that year.

The late Dr. de Sitter once remarked to me that American astronomers were, with a few conspicuous exceptions, a group of specialists; and he added with a smile that he did not know whether this was an element of weakness or of strength for the general progress of the science. His remark would have applied with much force to Frost, who persisted in devoting his energies to the spectroscopy of "early-type" stars to the practical exclusion of every other subject. Primarily for this purpose the Bruce spectrograph was constructed in 1900 largely from his specifications and under his supervision. With this instrument and with the able collaboration of Walter S. Adams, now director of the Mount Wilson Observatory, he measured the radial velocities of many "helium stars" or "Orion stars," as they were then called (now they are more logically designated as B-stars, following the Draper Classification), and discovered their most important characteristics. It was shown that their space velocities are small as compared with those of later-type stars and that there is a slight but unmistakable tendency for these stars to recede from our system as a whole, as if they formed an expanding group. These facts were later more fully developed by Campbell; their explanation is closely interwoven with recent important discoveries in astronomy and physics.

Frost also showed from changes in radial velocity that a surprising number of B-type stars are close binary systems, perhaps as many as one in every three. On several occasions I have witnessed his discovery of such a binary from a single photograph of its spectrum. This sounds like an impossibility, but the explanation is simple. Even in those days (around 1904) he was extremely nearsighted, and could see well an object not more than an inch from his eye; thus, as he used to say, by simply pushing his glasses up he always had at his disposal a magnifying power of about ten diameters. After he had secured a spectrogram and developed it the next morning, he would

examine it in this way, sometimes before it was dry. If he saw the lines considerably displaced from their normal positions, he knew that it was extremely unlikely that this was because of the star's large space velocity, since, as we have said, he had found that such velocities are always small for B-type stars; the displacements must then be due to orbital motion, and so indeed they invariably proved to be when later he could examine a series of plates of that star.

Frost's place in astronomy is not to be judged on the basis of his researches alone. We have already mentioned his translation of Scheiner's work and the part this translation played. For more than thirty years his was the chief responsibility for editing the *Astrophysical Journal,* "an international review of spectroscopy and astronomical physics," founded in 1895 by Hale and Keeler, and now in its eighty-first semiannual volume. One might say of Frost as Frost used to say of Burnham, "he is the best skeptic I know." As a result of this quality of judicious conservatism, the *Astrophysical Journal* has had little to regret in the way of hasty or ill-advised publication. In addition, he had an unusually sensitive feeling for language, which showed itself not only in his English but quite as well in German and nearly as well in French.

The last years of his life form a sad story, but an inspiring one as well. From early childhood he had had trouble with his eyes. This became acute by 1907 and necessitated long periods of complete rest for his eyes. In 1915 the retina in one eye became detached and within a few months he completely lost the sight in this eye, never to regain it. A few years later a cataract began to form in his other eye and grew worse and worse until he became totally blind. In spite of this heavy handicap, he managed for several years to continue his work as director of the observatory, but finally felt compelled to retire in 1933.

In the first year of his retirement he dictated to his wife, and dedicated to her, his autobiography, under the title "An Astronomer's Life."[1] The volume is important as a contribution to the history of present-day science. His story is told with fascinating charm, and I for one found it impossible to put it down before I had finished it. It is much more than a setting down of facts or a collection of well-told stories. As a record of courage and good sportsmanship in the face of one of life's severest disasters it can not fail to move every reader. In all his years of complete darkness he never lost his sense of humor. To the last he had a way of ignoring his blindness in conversation and whimsically using terms and expressions that one should ordinarily expect only from those who can see.

Early in April of this year Frost went to a Chicago hospital for observation. The cause of his ailment was diagnosed as gallstones. After some hesitation on account of his age (he was in his sixty-ninth year), an operation was performed on May 6. His condition improved for a few days but then his strength rapidly waned until the end came on May 12.

Among the honors that came to him were honorary degrees from Dartmouth and Cambridge; membership in the National Academy of Sciences, the American Philosophical Society and the American Academy of Arts and Sciences; honorary membership or the equivalent in the Royal Astronomical Society (London), Societa degli Spettroscopisti Italiani, astronomical societies in Mexico, Canada and Russia.

Dr. Frost was married in 1896 to Mary Hazard, of Boston; she and their three children survive him, as does his elder brother, who, like their father before them, is a professor in the Dartmouth Medical School.

FRANK SCHLESINGER
YALE UNIVERSITY OBSERVATORY
JUNE 4, 1935

[1] Houghton Mifflin Company, Boston and New York.

REGINALD OLIVER HERZOG

R. O. HERZOG was born in Vienna in 1878. His father was a newspaperman. After finishing his secondary education, Herzog studied chemistry at the University of Vienna under Lieben and there took his doctor's degree with a paper on organic chemistry. His interest, however, was at that time in physiological chemistry and so he went first to Heidelberg, where he worked in the Physiological Laboratory under Kossel, then to Utrecht and to Kiel. His first papers of this interval (1902–1905), nine in number, were concerned with straight physiological chemistry. But soon his interest branched out. He started to work on fermentation and the action of fungi. That led him deeper into industrial questions and he published papers on the theory of tanning and disinfection. On the other hand, he began to apply the methods of physical chemistry to ferment reactions, studying their kinetics and the influence of temperature upon them. In the meantime, he had moved to the Technische Hochschule at Karlsruhe, where he became first privatdozent, then ausserordentlicher (associate) professor. At that time, Haber was professor of physical chemistry there, working on the synthesis of ammonia. With him, Herzog formed a friendship that lasted until Haber's death in 1933.

In Karlsruhe, Herzog continued along his previous lines (physiological chemistry in general, fermentation), but he started also on two new subjects that were to occupy him through the rest of his life. He attempted to get a better insight into the constitution of the natural substances, many of which are colloidal, by physico-chemical methods. With this in mind, he instigated a number of experimental and theoretical

investigations on diffusion. Making use of recent formulas of Einstein, he showed how it was possible to use the diffusion coefficient to determine the size of large molecules. Secondly, he got interested in the connection between chemical structure and physical properties. He translated the text-book of Smiles with that title from the original English; this became the standard work on the subject in German. After a short stay in Berlin, he was called in 1912 as full professor of mycology to the Technische Hochschule in Prague. But at the outbreak of the war his friend Haber, who in the meantime had become director of the Kaiser Wilhelm Institut for Physical Chemistry in Berlin, had him transferred there, where he worked on the improvement of the cloth and rubber material for gas masks. After the war he returned shortly to Prague, but in 1921 he was made director of the newly founded Kaiser Wilhelm Institut of Textile Chemistry. Here, as direct neighbor of Haber, he found himself in an ideal position. He was rid of the teaching he disliked. He was at the head of a laboratory, which he could organize, and at the same time he could work with industry, consulting and advising. His laboratory devoted half its work to technical questions, but half of it was devoted to purely scientific problems. Herzog succeeded in picking out young men who were destined to make their place in chemistry. Ewald, now professor in Stuttgart; Polanyi, now professor in Manchester; Mark, now professor in Vienna; Schmid, now in Freiburg in Switzerland; Smekal, now in Halle; Bergmann in Dresden, now in New York, and Weissenberg worked there. The problems selected bore on the fundamentals of textile structure as the clue to its properties. And so Herzog started the new tool, x-ray investigation of structures, on natural organic matter. The concept of fiber structure (Polanyi) was born here, and investigations on the structure of textile-fibers, wood and chitin were made.

A large group of investigations centered around the strength of fibers and gave rise to a group of papers on gliding and stretching of metals, which have contributed greatly to our understanding of the strength of metals. Of course, purely chemical problems were not neglected.

In recent years, the depression forced the curtailment of the purely scientific work, as the institute was mainly supported by industry. A large part of Herzog's time began to be occupied with the search for money to keep the institute up. But he did not neglect his own work and turned again his attention to the fundamental question of the structure of glasses and liquids, to the nature of viscosity and the like. He was also editor of an Encyclopedia on the technology of textile materials. His list of publications contains 52 articles for 1901–1914, 91 articles from 1921 on.

In the fall of 1933 he was retired from his position and accepted a professorship at the reorganized University of Istanbul (Constantinople, Turkey). At the beginning he felt the change very strongly, but seemed after some time to get better accommodated to it. In the beginning of 1935 Mrs. Herzog, who was suffering from a chronic knee ailment, and he went to Zurich in Switzerland for medical treatment. His own health was bad. Since the war he had been suffering deeply under the general conditions of the world. His idealism and scientific attitude felt deeply hurt by the hate and unreason rampant everywhere. In a fit of depression he took his life on February 4.

K. F. HERZFELD

THE JOHNS HOPKINS UNIVERSITY

MEMORIAL TO CHARLES DARWIN

PERMISSION to erect a memorial to Charles Darwin in the Galapagos Islands to commemorate his visit there 100 years ago, according to *The Christian Science Monitor,* has been granted to the Darwin Memorial Expedition by President Velasco Ibarra of Ecuador. The memorial, it was indicated, will be in the form of a scientific research station, the establishment of which "would make available to present-day natural scientists from all over the world an opportunity to study at first-hand Galapagos flora and fauna, whose primitive state is to-day as completely remote from the encroachments of civilization as it was upon Darwin's epochal sojourn there a century ago."

In addition to the scientific research station, a monolith will be erected on Chatham Island, one of the most important of the group. This monolith will bear commemorative bas-reliefs on each of its four faces and will be topped by a replica of the bronze bust of Darwin now in the hall of biology of the American Museum of Natural History. Dedication of the memorial has been fixed for September 6.

Arrangements for the memorial were made with the Government of Ecuador by Dr. B. W. von Hagen, leader of the expedition, who is now in Ecuador carrying on ethnological, geographical and biological surveys of the coast and hinterland.

RECENT DEATHS

EDWARD SALISBURY DANA, tutor and professor of physics at Yale University from 1874 until his retirement as professor emeritus in 1918, curator of mineralogy from 1875 to 1920, died on June 16, in his eighty-sixth year.

DR. LEÓN M. GUERRERO died on April 13. The Executive Board of the National Research Council of the Philippine Islands have passed resolutions in his memory which refer to his work in the following

terms: "Dr. León M. Guerrero was a Filipino scientist who rendered invaluable services in science to his country and his people in different epochs of Philippine history. Through his untiring efforts and painstaking research great achievements have been recorded in the study of Philippine medicinal plants."

SCIENTIFIC EVENTS

THE DEDICATION OF THE RICHARD T. FISHER MEMORIAL

ON June 9, beneath a cluster of ancient white pine, hemlock and hardwood—a most appropriate setting—President James B. Conant of Harvard University assisted in the dedication of a bronze memorial tablet to the late Professor R. T. Fisher. The ceremony was held at noon, on the Tom Swamp Tract of the Harvard Forest at Petersham, Mass. Despite the intermittent heavy rain, some one hundred and fifty friends, relatives, alumni of the Harvard Forest School and professional colleagues were present. The site for the memorial is a lovely woodsy spot, and is regarded as singularly fitting, inasmuch as Professor Fisher often came there to study and to photograph the interesting wild life in the game sanctuary of which this area is a part.

John S. Ames, '01, president of the Forest School Alumni Association and donor of the lands making up the Harvard Forest, presided, and in a brief address told how the tract was obtained and how it had become the oldest managed forest in the United States. He further mentioned how justly proud Professor Fisher was of its growth and of the increasing number of visits made by technical foresters from various portions of the world.

Henry H. Tryon, '12, director of the Black Rock Forest at Cornwall-on-Hudson, N. Y., and chairman of the Fisher Memorial Committee, spoke briefly of the well-nigh unanimous admiration and loyal affection which the alumni held for their former director, and added that there could be no more fitting place for the memorial than this spot, where he loved to come.

President Conant, before lifting the simple spray of spruce and larch which covered the tablet, touched perhaps the true dedicatory note: "Professor Fisher was the real creator of this forest. His untimely death prevented the completion of many well-laid plans that he had in the making. His death will even more closely unite the forest with Harvard University. Professor Fisher was continually laying plans for the advancement of this wonderful work; it was only a short time before his sudden death that he discussed with me at some length the future of the work here. These plans now rest with us to carry out. On behalf of the Governing Board of Harvard University I accept this memorial with a full sense of the responsibility which is implied therein, and with a renewed gratitude for Professor Fisher's outstanding work."

Those present included Mr. and Mrs. Peter Frothingham, Mr. and Mrs. William James, Henry James, Dr. Thomas Barbour, Dr. E. G. Stillman, E. S. Bryant, Dean George H. Chase, A. H. Upham, Wm. G. Howard, state forester of New York, H. O. Cook, state forester of Massachusetts, Mrs. George R. Agassiz, Dr. R. H. Wetmore, Professor Henry V. Hubbard, Dr. John C. Phillips, Professor Irving W. Bailey, Professor Harlow Shapley, and many others.—*A Correspondent.*

THE SAN FRANCISCO MEETING OF THE AMERICAN CHEMICAL SOCIETY

THE rise of the chemical industry on the Pacific Coast will be emphasized at the ninetieth meeting of the American Chemical Society, which will be held in San Francisco from August 19 to 23. Chemists from all over the country will participate. Petroleum, wine-making, vitamins and new uses for wood will be special fields of discussion.

Dr. Edward C. Franklin, professor emeritus at Stanford University, known for his researches in liquid ammonia solutions, which opened up a new field in organic chemistry, has been appointed honorary chairman of the convention. Professor Franklin is the holder of the Willard Gibbs Medal. Dr. Arthur Lachman, of the University of California, has been named general chairman.

Most of the professional divisions will hold sessions. The Division of Agricultural and Food Chemistry and the Division of Industrial and Engineering Chemistry will conduct a joint symposium on the chemistry and technology of wine.

A joint session of the Division of Petroleum Chemistry and the Division of Industrial and Engineering Chemistry will discuss "Solvent Extraction and Solvent Dewaxing of Lubricating Oils." The Petroleum and Gas and Fuel Chemistry Divisions will sponsor a symposium on the utilization of natural gas hydrocarbons.

Wood as the raw material for chemical commodities will be the subject of another symposium of the Division of Industrial and Engineering Chemistry. Joint symposia on vitamins and the minor elements of animal nutrition are planned by the Divisions of Medicinal Chemistry, Biological Chemistry and Agricultural and Food Chemistry. Professor Roe E. Rem-

ington, of the Medical College of South Carolina, will preside.

Sessions will be devoted to other fields of chemistry, including cellulose, colloids, gas and fuel, chemical education, paint and varnish, sugar and physical and inorganic chemistry. The presidential address will be delivered by Professor Roger Adams, of the University of Illinois.

Dr. William Albert Noyes, emeritus director of the laboratories of the University of Illinois, will receive the Priestley Medal, the highest honor of the American Chemical Society, which is bestowed every three years "for distinguished service to chemistry." The American Chemical Society Award in Pure Chemistry of $1,000 will be presented to Dr. Raymond M. Fuoss, of Brown University.

GRANTS IN AID OF RESEARCH FOR 1936 OF THE AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

FROM various donors, the association has received in the past funds with the provision that the income thereof be used in making small grants for the encouragement of research. The allotment of these funds is assigned to the Committee on Grants. Within recent years, the committee has been inclined to prefer recommending the appropriation of sums to aid in the completion of important projects already initiated or to supply apparatus or facilities in circumstances where adequate funds are not otherwise available. The committee has ordinarily at its disposal the sum of $3,000.

Individual grants have previously been limited to amounts of less than $500, and many smaller sums have been useful in meeting emergency needs or such as are not covered by other agencies. Applications for grants are filed on special blanks which may be secured from the office of the permanent secretary. It is important that each application be supported by letters from at least two sponsors who are personally acquainted both with the applicant and with the project and are able to speak specifically regarding both items.

The membership of the committee for the current year is as follows: Arthur H. Compton (1937) (for physics), University of Chicago; J. B. Macelwane (1936) (for geology), St. Louis University; William Crocker (1935) (for botany), Boyce Thompson Institute; Philip Fox (1935) (for astronomy), Adler Planetarium; McKeen Cattell (1935) (for medical sciences), Cornell Medical School; M. Gomberg (1935) (for chemistry), University of Michigan; C. C. Little (1937) (for zoology), Jackson Memorial Laboratory; Walter R. Miles (1936) (for psychology), Yale University. The committee prefers that all correspondence be addressed to the permanent secretary and not to individual members. The fiscal year of the association opens on October 1 and closes on September 30 following. All grants not utilized within the year normally revert to the treasury of the association on October 1.

Applications for grants for 1936 must be received at the permanent secretary's office in Washington, D. C., on or before October 30. Reports which are incomplete or late in arrival can not be considered for the year 1936. The report of the committee is laid before the executive committee and the council at the annual meeting in December and payment of approved grants is made by the treasurer following that meeting. Unused portions of grants should be returned on October 1 of each year.

Publications including results obtained by virtue of the assistance rendered through grants should contain due acknowledgment of the aid furnished by the association. Recipients of grants are expected to make at least one report, which should be filed with the permanent secretary not later than October of the year for which the grant was made. In case completion of the report is delayed, notice should be sent to the permanent secretary's office, and a statement of the results obtained in the research should be made at the time the report is filed.

HENRY B. WARD,
Permanent Secretary

BIRTHDAY HONORS OF THE KING OF ENGLAND

As cabled from Europe and announced in SCIENCE the birthday honors of King George of England included the Order of Merit of the British Empire conferred on Sir Frederick Gowland Hopkins, president of the Royal Society, "in recognition of his eminent services to biochemistry, especially in connection with the discovery of vitamins." A baronetcy was conferred for public services on Dr. Evan Williams, president of the Mining Association of Great Britain.

Other honors include:

Knights Bachelors:

Noel Ashbridge, chief engineer of the British Broadcasting Corporation.

Professor Joseph Barcroft, professor of physiology, University of Cambridge.

Dr. Arthur John Hall, emeritus professor of medicine, University of Sheffield, for distinguished service to medicine and medical science, with special reference to problems of the health of industrial workers.

John Hepburn Milne Home, vice-chairman, Advisory Council to Department of Agriculture for Scotland, for services to agriculture.

Patrick Playfair Laidlaw, pathologist to the Medical

Research Council, for distinguished service to medical science.

Arthur Pugh, general secretary of the Iron and Steel Trades Confederation and of the British Iron, Steel and Kindred Trades Association.

The Order of Knight Companion of the British Empire:

Dr. John Cunningham M'Lennan, professor emeritus and visiting professor of physics, University of Toronto, for fundamental discoveries in physics and for scientific services.

The Order of Companion of the Bath:

Dr. William Thomas Calman, keeper of zoology, British Museum of Natural History; president of the Linnean Society of London.

Dr. Frank Sturdy Sinnatt, director of fuel research, Department of Scientific and Industrial Research.

AWARDS IN THE SCIENCES OF THE AMERICAN MEDICAL ASSOCIATION

IN the Class I exhibits at the meeting of the American Medical Association at Atlantic City the gold medal was awarded to an exhibit showing ergotocin, a crystalline form of the active principle in ergot, discovered after three years of research by the cooperative efforts of three physicians, Dr. M. Edward Davis, Dr. Fred L. Adair and Dr. Gerald Rogers, and two chemists, Dr. M. S. Kharasch and Dr. Romeo R. Legault.

The silver medal was awarded to Drs. Leonard G. Rowntree, J. H. Clark and Arthur Steinberg, of the Philadelphia Institute for Medical Research, and Dr. A. M. Hanson, Faribault, Minn., for original investigations on the biological effects of the thymus and pineal glands.

The bronze medal was given to Drs. Jane Sands Robb, J. G. Fred Hiss and R. C. Robb, for original investigations on heart muscle-bundle physiology and experimental coronary lesions.

Certificates of merit were awarded to Dr. Bede J. Harrison, of the Vancouver General Hospital; Drs. Aaron E. Kanter, Carl P. Bauer and Arthur H. Klawans, of Rush Medical College, University of Chicago, and Drs. Isaac Schour and A. G. Brodie, of the University of Illinois College of Dentistry.

The gold medal in Class II was awarded to Drs. Stuart Harrington and Willis S. Lemon, of the Mayo Foundation for Medical Education and Research, Rochester, Minn., "for excellent presentation of an exhibit illustrating the surgical treatment and clinical manifestations of various types of diaphragmatic hernia [inverted stomach] and intra-thoracic tumors."

The silver medal, given for exhibits that do not exemplify purely experimental studies, was given to Drs. David W. Mackenzie and Alexander B. Wallace, of the Royal Victoria Hospital, Montreal, for their exhibit on lymphatic studies. The bronze medal went to Dr. James Harold Mendel of Philadelphia for his exhibit on eardrums.

SCIENTIFIC NOTES AND NEWS

THE summer meeting of the American Association for the Advancement of Science opens at the University of Minnesota, Minneapolis, on June 24, under the presidency of Dr. Karl T. Compton, president of the Massachusetts Institute of Technology. The opening session on Monday evening will be a joint meeting with the Minnesota State Medical Association with an address on "Diseases of the Blood," by Dr. W. P. Murphy, which will be followed by a reception given by Dr. Lotus D. Coffman, of the University of Minnesota, and Mrs. Coffman. The Maiben lecture will be given on Tuesday evening by Dr. Richard P. Strong, and there will be other evening lectures by Dr. Isaiah Bowman, Dr. W. F. G. Swann and Dr. Philip Fox. The full preliminary program will be found in the issue of SCIENCE for May 24.

THE Barnard gold medal "for meritorious service to science" of Columbia University has been awarded to Dr. Edwin P. Hubble, astronomer of the Mount Wilson Observatory. This medal was founded in 1889 and is awarded every five years on the recommendation of the National Academy of Sciences.

THE gold medal of the Linnean Society of London was presented at its anniversary meeting on May 24 to Dr. David Prain, until his retirement in 1922 director of the Royal Botanic Gardens at Kew, "in recognition of his services to botany." Dr. W. T. Calman delivered the address of the president on "The Meaning of Biological Classification."

THE council of the Royal Empire Society has awarded its gold medal for 1935 to Sir Wilfred Grenfell, "in recognition of his services to the Empire and of the excellence of his book, 'The Romance of Labrador.'"

THE degree of doctor of laws was conferred at the commencement of the University of Pennsylvania on Dr. Charles Russ Richards, mechanical engineer, retiring president of Lehigh University, and on Dr. Isaiah Bowman, director of the American Geographical Society, chairman of the National Research Council and president-elect of the Johns Hopkins University.

HONORARY degrees conferred by Wesleyan University included the doctorate of science on Dr. George

H. Whipple, professor of pathology of the School of Medicine and Dentistry at the University of Rochester.

THE degree of doctor of engineering has been conferred by the Polytechnic Institute of Brooklyn on Dr. Charles F. Scott, professor emeritus of electrical engineering at Yale University, and the degree of doctor of science on Professor Roger Adams, head of the department of organic chemistry at the University of Illinois.

At the commencement of Temple University, Philadelphia, the doctorate of laws was conferred on Dr. Edward Martin, emeritus professor of surgery at the University of Pennsylvania, and the doctorate of science on William H. Meese, vice-president of the Western Electric Company, Baltimore.

THE degree of doctor of laws was conferred by New York University on June 10 on Frederick Trubee Davison, president of the American Museum of Natural History.

OFFICERS of the American Medical Association were elected on June 13 at the Atlantic City meeting as follows: *President-elect,* Dr. J. Tate Mason, of Seattle; *Vice-president,* Dr. Kenneth M. Lynch, of Charleston, S. C.; *Secretary,* Dr. Olin West, of Chicago (reelected); *Treasurer,* Dr. Herman L. Kretschmer, of Chicago (reelected); *Speaker of the House of Delegates,* Dr. Nathan B. Van Etten, of New York; *Vice-speaker,* Dr. H. H. Shoulders, of Nashville, Tenn. The house of delegates voted to accept the invitation to hold the 1936 convention in Kansas City, Mo.

THE officers, executive committee and members of the Division of Geology and Geography, National Research Council, for the year beginning July 1 are as follows: *Chairman,* Edson S. Bastin; *Vice-chairman,* W. L. G. Joerg; *Executive Committee,* Edson S. Bastin, W. L. G. Joerg, A. F. Buddington, Charles Butts, W. F. Foshag and Robert S. Platt; *Representatives of Societies,* Donald C. Barton and A. F. Buddington, Geological Society of America; W. F. Foshag, Mineralogical Society of America; Charles Butts, Paleontological Society; C. F. Marbut and Robert S. Platt, Association of American Geographers; W. L. G. Joerg, American Geographical Society; Thomas B. Nolan, Society of Economic Geologists; F. H. Lahee, American Association of Petroleum Geologists; *Members at Large,* Florence Bascom, Edson S. Bastin and Ellsworth Huntington.

AT the seventeenth annual meeting of the American Society of Mammalogists held at the Carnegie Museum, Pittsburgh, from April 30 to May 4, officers elected for the coming year are: *President,* H. E. Anthony; *Vice-presidents,* Joseph Grinnell, E. A. Preble; *Recording Secretary,* Robert K. Enders; *Corresponding Secretary,* William H. Burt; *Treasurer,* Mrs. Viola S. Snyder; *Editor,* A. Brazier Howell; *Directors,* class of 1935–1937, Remington Kellogg, A. Brazier Howell, W. E. Saunders, Harold J. Coolidge, Jr., William J. Hamilton, Jr. Seventy-one members were present at the meeting. These came from thirteen states and two Canadian provinces, and thirty-five papers, dealing with various phases of mammalogy, were presented. The next annual meeting will be held at the Academy of Natural Sciences in Philadelphia.

AT the annual installation banquet of the Western Reserve University Chapter of the Society of the Sigma Xi, the following officers for 1935–36 were installed: *President,* J. P. Visscher; *Vice-president,* C. J. Wiggers; *Secretary,* W. M. Krogman; *Treasurer,* Frank Hovorka. The address of the evening, under the joint auspices of the Brush Foundation and the Society of Sigma Xi, was given by Professor C. U. Ariëns Kappers, director of the Central Institute for Brain Research, Amsterdam, on "The Brain of Prehistoric and Recent Races of Man."

THE Botanical Society of New Orleans held its annual dinner on June 7, and elected the following officers for the year 1935–36: Ronald B. Craig, associate forest economist of the Southern Forest Experiment Station, *president,* to succeed Dr. William T. Penfound, professor in the department of botany of Tulane University; James M. McArthur, director of nature study and gardening of the Orleans parish public schools, *vice-president;* Dr. Minna F. Koch, morphologist, *secretary,* and Philip C. Wheeler, associate forest economist, *treasurer.*

DR. LINUS H. JONES, assistant research professor of botany at the Massachusetts State College, was elected secretary of the New England section of the American Society of Plant Physiologists at the recent meeting at the University of New Hampshire. Dr. Walter S. Eisenmenger, head of the department of agronomy, was reelected to the executive board.

PROFESSOR PIETER ZEEMAN has retired from the professorship of physics and directorship of the Physical Institute of the University of Amsterdam, having reached his seventieth birthday. *Nature* reports that in order to allow his many admirers an opportunity of showing their appreciation of his important contributions to science, it is proposed that a jubilee volume be published, to which thirty distinguished physicists have already promised contributions, and that a Zeeman fund, a Zeeman medal or some similar method of encouraging research be founded. A general committee with representatives from all parts of the world has been formed with an executive commit-

tee under Professor J. D. van der Waals, Jr., with T. L. de Bruin, of 33 Gerard Terborgstraat, Amsterdam S., as secretary and treasurer to carry out the proposals, and an appeal is now made for funds in support of the scheme.

AT Harvard University, Dr. John Hasbrouck Van Vleck has been appointed to a professorship of mathematical physics, Dr. Harry Rowe Mimno, tutor, has been made assistant professor of physics, and Frederick Vinton, tutor, has been appointed instructor in physics and communication engineering and tutor in the division of physical sciences.

AT the University of Colorado, Dr. P. G. Worcester has been promoted from acting head to head of the department of geology; Dr. Warren O. Thompson, from assistant to associate professor of geology; Dr. Howard Stagner, from assistant to instructor in geology, and Dr. L. O. Quam, from part-time to full-time instructor in geography.

DR. HORACE J. FRASER, research geologist with the International Nickel Company at Sudbury, Ontario, has been appointed assistant professor of mineralogy and mineragraphy at the California Institute of Technology.

DR. HENRY KLEIN, formerly associated with Dr. E. V. McCollum at the School of Hygiene and Public Health, the Johns Hopkins University, has been appointed to the staff of the Dental College of the University of Detroit.

AT the University of London, the chair of civil and mechanical engineering, King's College, has been filled by the appointment of Dr. C. H. Lobban, university reader in civil engineering at the college, and the chair of physiology, St. Mary's Hospital Medical School, by the appointment of Dr. A. St. G. J. McC. Huggett, reader in pharmacology and member of the department of physiology at the University of Leeds.

EDGAR SYDENSTRICKER was appointed scientific director of the Milbank Memorial Fund on June 1. From 1920 to 1928 he was in charge of statistical research in the U. S. Public Health Service and since then has been consulting statistician to the service and director of the research staff of the Milbank Fund.

DR. J. G. HILDEBRAND, JR., a graduate of Columbia University, has recently joined the staff of Gustavus J. Esselen, Inc. He will have charge of a new laboratory devoted to the application of electronics to industry. He will also assist in the application of the principles of motion picture photography to the recording and interpretation of the results of scientific investigations.

THE British Minister of Health and the Secretary of State for Scotland have appointed an Advisory Committee with the following terms of reference: To inquire into the facts, quantitative and qualitative, in relation to the diet of the people, and to report as to any changes therein which appear desirable in the light of modern advances in the knowledge of nutrition. The chairman of the committee is Lord Luke. Members include Professor E. P. Cathcart, Sir F. Gowland Hopkins, Professor E. Mellanby and Sir John Boyd Orr.

DR. FRANCIS E. LLOYD, emeritus professor of botany at McGill University, will visit Capetown and Australia during the next fifteen months for the particular purpose of studying Utricularia in the field. He will visit Brisbane in the summer season and move south and west, so as to spend some months in Perth, Southwest Australia, during the following winter season.

GUESTS for the summer at the Morris Biological Farm of the Wistar Institute of Anatomy include Dr. O. Larsell, professor of anatomy at the University of Oregon, who will continue his studies on the development of the nervous system of the opossum; Dr. Edward L. Corey, assistant professor of physiology at the University of Virginia, who will work on the central nervous system by operative procedures on pregnant rats, and Dr. Rush Elliott, associate professor of comparative anatomy at Ohio University, who will carry on neurological work with Dr. A. W. Angulo, associate member of the institute.

DR. KIRTLEY F. MATHER, professor of geology at Harvard University, gave the baccalaureate address at Purdue University.

DR. JESSE HAYES WHITE, formerly professor of psychology at the University of Pittsburgh and ex-president of James Millikin University, gave the commencement address at Upper Iowa University on June 10.

SIR ARTHUR EDDINGTON gave an address on "The Physics of the Sun" on the occasion of the dedication on June 11 of the new solar telescope provided for Professor H. H. Plaskett at the University Observatory, Oxford.

THE annual meeting of the Federation of American Societies for Experimental Biology will be held in Washington, D. C., from March 25 to 28, 1936.

THE seventh annual meeting of the Society of Rheology will be held in New York City at the Bell Telephone Laboratories on October 11 and 12. Special features of this meeting will be the two symposia which are being planned on the rheological aspects of rubber and plastics. The committee in charge of the de-

velopment of the plastics symposium are: Dr. E. O. Kraemer, Marshallton, Del., and H. F. Wakefield, Bakelite Corporation. The rubber symposium is being developed by Dr. Melvin Mooney, U. S. Rubber Products Company, and J. H. Dillon, Akron, Ohio. In addition, a general symposium on rheology is being developed by Dr. E. C. Bingham, Lafayette College, and Dr. A. Nadai, of the Westinghouse Electric and Manufacturing Company. Authors having papers which they wish to present at this time are invited to address the specified committees.

FINAL sessions of the tenth annual meeting of the Hawaiian Academy of Science were held on the evenings of May 16 and 17 at the University of Hawaii in Honolulu. Previous sessions for the presentation of papers had been held on October 24 and 25. The annual dinner was held on May 18 at the Pacific Club, followed by an address on Hawaiian birds by the retiring president, Edwin H. Bryan, Jr., curator of Collections of the Bishop Museum. The following officers were elected for the year 1935–1936: *President,* Chester K. Wentworth, geologic engineer, Board of Water Supply; *Vice-president,* Harold A. Wadsworth, soil physicist, School of Tropical Agriculture, University of Hawaii; *Secretary-treasurer,* Beatrice H. Krauss, assistant plant physiologist, Experiment Station, Pineapple Producers' Cooperative Association; *Council,* in addition to officers: E. H. Bryan, Jr., past president, *ex officio;* E. L. Caum, assistant botanist, Experiment Station, Hawaiian Sugar Planters' Association, 1935–1937; Walter Carter, entomologist, Experiment Station, Pineapple Producers' Cooperative Association.

ACCORDING to a United Press dispatch, three hundred foreign astronomers are expected at Paris between July 9 and 17 to attend the biennial congress of the International Astronomical Union. Presiding over the sessions of the congress will be Professor Frank Schlesinger, director since 1920 of the Yale University Observatory. He also heads the executive committee, which draws up the agenda. Count de la Baume Pluvinel, who is president of the French National Committee of Astronomy, is arranging for the practical aspects of the congress. He is aided by Jules Baillaud, astronomer of the Paris Observatory. Thirty nations are to be represented, as was the case in 1932, when the congress was held at Harvard University.

THE Division of Medical Sciences of the National Research Council will hold a special meeting in November, 1935, for the consideration of applications for grants-in-aid in this field. Applications to be considered at this meeting must be on file with the Secretary of the Committee on Grants-in-Aid, Dr. Clarence J. West, not later than October 1, 1935. Applications received after October 1 and prior to February 15, 1936, will be acted upon at the next regular meeting of the committee in March, 1936.

E. J. BUFFINGTON, Chicago steel manufacturer, has given $100,000 as an endowment to Vanderbilt University. Half of the endowment is to be used as a general fund and the other half is to endow a chair in the school of religion to be named the Drucilla Moore Buffington chair in memory of his late wife.

STANFORD UNIVERSITY has received a gift of $1,000 from the widow of James Perrin Smith, to be used for the maintenance and improvement of his library on the subject of fossil Cephalopoda. The library itself was presented by Mrs. Smith to the library of the university soon after the death of Dr. Smith in 1931.

JULIAN W. LOW, of the department of geology of the University of Colorado, has recently completed a mold for the striking of plaster casts of a relief model of the western half of Boulder County. The model is 50 inches by 58 inches in size, with a horizontal scale of two inches to the mile, and a vertical scale of one inch to one thousand feet. It includes the western edge of the Great Plains and all the intervening country to and a little beyond the Continental Divide. The foothills ridges, the canyon cutting below the Rocky Mountain peneplain, the peneplain remnants themselves and the glaciation near the Continental Divide are some of the topographic features brought out by this model.

DISCUSSION

THE NEW ACTIVE PRINCIPLE(S) OF ERGOT

THE arguments advanced by Dudley and Moir in connection with their recent suggestion[1] that *ergotocin* be recognized as identical with *ergometrine* and called by the latter name embody several misconceptions. For two of these the careless wording and erroneous placement of the footnote on p. 166 of our earlier publication with Davis, Adair and Rogers in the *American Journal of Obstetrics and Gynecology* (29: 155–67, February, 1935) were undoubtedly responsible. This footnote was intended to announce that Eli Lilly and Company could supply commercial quantities of the pure, active principle, ergotocin—not "an impure preparation," as assumed by Dudley and Moir. Indeed, at the time the announcemnt actually appeared the company had been preparing the pure principle

[1] SCIENCE, 81: 2110, 559, June 7, 1935.

for a period exceeding two months and had accumulated records of tests on over 200 human patients. Since Eli Lilly and Company was actually preparing pure ergotocin it might justifiably have continued to apply that name to its commercial product. Actually, however, the latter has been given the trade name, "Ergotrate."

The question as to whether or not ergotocin is an "alkaloid" seems to us to be essentially meaningless, since there are no definite chemical criteria by which a substance may be characterized as alkaloidal or non-alkaloidal. In the earlier paper already cited we called attention to the loose usage of the term "alkaloid," and made it clear that our own use of the term "non-alkaloidal" was intended merely as exclusive of the previously known ergot "alkaloids" rather than as chemically descriptive.

It is possible, though not altogether obvious, that the principle responsible for the physiological activity of ergometrine is identical with ergotocin. It is, however, obvious that ergometrine, as described by Dudley and Moir, is not identical with ergotocin. Our own analyses of pure ergotocin and several of its salts indicate the empirical formula $C_{21}H_{27}N_3O_3$ (C, 68.41 per cent.). (For details, as well as for a discussion of the cleavage products of ergotocin, see the June number of the *Journal* of the American Chemical Society.) Dudley and Moir have announced that ergometrine has a carbon content of 71.46 per cent. The discrepancy would seem great enough to survive any "slight modifications" necessitated by "more drastic purification" of an essentially pure substance. The physiological properties attributed to ergotocin and to ergometrine are similar but evidently differ in degree. The oral dose of ergometrine recommended by Dudley and Moir for human patients is 0.5–1.0 mg; ergotocin is uniformly effective in oral doses of 0.25–0.30 mg. On the whole, the assumption of identity of the active principles appears premature; moreover, that assumption would seem to lead inevitably to the conclusion that ergometrine is impure or partially inactivated ergotocin.

The implication that the chemical investigation of ergot by the present authors was suggested or inspired by Dr. Moir's American addresses seems to us irrelevant to the issue raised. As a matter of strict historical fact, however, our interest in ergot had quite another origin. Neither of us had the pleasure of hearing Dr. Moir during his American visit, nor did we, indeed, hear of him until after we had succeeded in separating ergotocin from the "known ergot alkaloids" late in 1923.

M. S. KHARASCH
R. R. LEGAULT

THE UNIVERSITY OF CHICAGO

THIOBARBITURATES

THE report of the hypnotic action of a series of barbituric acid derivatives by Fischer and von Mering[1] in 1903 led to the introduction of barbituric acid compounds into medical practice. Hundreds of substituted barbituric acids and their soluble salts, alone and in various combinations, have been prepared since then in the unceasing search for better products. Some of these compounds have been found to possess valuable therapeutic properties, and their use is rapidly increasing.

Barbiturates may be prepared by condensing urea (or a substituted urea) with derivatives of malonic ester. In a similar way we have prepared a series of thiobarbiturates, using thiourea (or a substituted thiourea), instead of urea. Only a few thiobarbiturates have been previously reported and these have been used merely as intermediates in the preparation of barbituric acid compounds.

There is almost complete lack of pharmacological, clinical and toxicological information in the literature on thiobarbiturates. This may be due to the findings of Fischer and von Mering that the administration of 120 mg per kilo of the sulfur analogue of barbital to a dog produced deep sleep, followed by death. This finding was broadcast by Fraenkel,[2] who deduced therefrom that the presence of sulfur imparts to diethylthiobarbituric acid a pronounced toxic character.

The authors have made and studied a number of thiobarbiturates, finding that they show promise as sedatives. They produce quiet, natural sleep and are free from side actions and from the after-effects observed following the use of their oxygen analogues. This work is being continued and will be reported in detail elsewhere.

ELLIS MILLER
JAMES C. MUNCH
FRANK S. CROSSLEY

SHARP AND DOHME
PHILADELPHIA, PA.

THE USE OF THE TERM POCONO

IN a recent article George H. Chadwick asks "What is Pocono?",[1] a question which has of late been troubling some stratigraphers in Pennsylvania. From Mr. Chadwick's article it appears that the original definition meant to include certain beds found under-

[1] E. Fischer and J. von Mering, Therap. d. Gegenw., 101: 97, 1903.
[2] S. Fraenkel, "Die Arzneimittel-synthese," 6th ed., 1927, p. 510.
[1] G. H. Chadwick, *Am. Jour. Sci.*, 5th ser., 29: 133–143, 1935.

lying the Pocono Plateau of eastern Pennsylvania. These beds, Mr. Chadwick has clearly demonstrated by both text and figure, may be of late Devonian rather than early Mississippian age, a perfectly reasonable belief in the light of recent changes in the interpretation of the Devonian of eastern New York and Pennsylvania. Therefore, the use of the term Pocono formation for these beds is inapplicable if it is also to include early Mississippian strata in other parts of Pennsylvania. But, paradoxically, the first published use of the term Pocono did not include the so-called Pocono of the Pocono Plateau. The first clear recognition of the formation, though under a different name, was that of Rogers[2] in his Vespertine or No. X formation:

> The Vespertine group of strata, the first of the carboniferons formations of the Appalachians, has a very wide distribution in Pennsylvania, encircling with a sort of outer girdle all the coal-fields, both the anthracite and the bituminous ones, of the State. It undergoes gradual but important changes of type, growing thinner and assuming a finer and finer texture in its materials as it spreads westward. Its orographic position is in the mountain-ridges and external escarpments of the table-lands which enclose or support the coal-fields; but, except in the northwestern district of the State, it does not immediately adjoin the conglomerates and sandstones of the coal-measures, but is separated from them by a greater or less thickness of the soft, umbral rocks, which fill either an intervening valley or an intermediate space on the coal-bearing table-lands.

From Pennsylvania southward this is essentially the definition of the Pocono as now in use,[3] and is equivalent to that officially recognized by the present Survey.[4] The first published use of the term Pocono as a stratigraphic term, in so far as the writers can ascertain,[5] is on the geologic maps of Bradford and Tioga counties, Pennsylvania, published in 1876. These were prepared by Andrew Sherwood under the direction of J. P. Lesley and accompany Volume G of the Pennsylvania Second Geological Survey. The text did not appear until 1878, and, curiously, does not use the term Pocono at all. On the map the formation is indicated as "X Pocono Sandstone" lying between "IX Catskill" and "XI Red Shale," but in the text is referred to as "White Catskill." This use accords with the Vespertine of Rogers. Not until 1877 did a fuller definition appear. In that year both Ashburner[6] and Franklin Platt[7] published definitions. They state that the term was proposed by Lesley to supplant Vespertine No. X of Rogers. As defined by both it is confined to beds between the "Catskill" and Mauch Chunk. But, Platt wrote:

> If No. IX be properly called the Catskill Formation because it forms the mass of mountains between the Hudson River and the Delaware, it is perfectly proper that the Gray Sandstone formation, No. X, next above it, should be called the Pocono formation, for it forms the mass of the great mountain plateau between the Delaware and Lehigh rivers.

Clearly, if Mr. Chadwick be correct, this definition is in error; and it is this to which he rightly objects, but the interesting fact remains that this is not the first use of the term. From these data it appears that Lesley, perhaps at a staff conference, certainly not later than 1876, proposed the term Pocono to replace Vespertine and intended it to be applied throughout the state wherever Vespertine had been used, whatever his type locality may have been. Such was the intent in the first use by Sherwood on two published maps of a region remote from the Pocono Plateau. His use is that which many subsequent writers adopted in applying the name Pocono in many parts of Pennsylvania, and it is in this very sense that the term Pocono is now accepted and used stratigraphically in the state and to the south. Its application to the plateau between the Delaware and Lehigh rivers, whatever Lesley's original intent, may be wrong and, if so, has been wrongly followed. But it seems reasonable that Lesley's original thought, even though he incorrectly dated the beds of the plateau, was to apply the name to the sandstone between the "Catskill" and Mauch Chunk, else the 1876 maps could not have appeared with his approval.

There seems no necessity for discontinuing the use of the name Pocono formation for the gray sandstones and conglomerates probably of early Mississippian age which overlie the highest recognized Devonian beds and help support the Allegheny Front, border much of the anthracite fields, produce prominent ridges in central Pennsylvania and appear as more or less flat-lying beds in the western parts of the state. But, in so doing, we must bear in mind the anomalous situation that the first published application of the term was not to a type locality of that name. Here we have a term derived from a type locality which turns out to be probably inappropriate, yet it was originally applied in print, not to that type locality, but to a different place but in the correct, original sense and intent. Subsequent stratigraphic studies may even

[2] Henry D. Rogers, "The Geology of Pennsylvania," Vol. I, 142–143, 1858.

[3] D. White, *Am. Jour. Sci.*, 5th ser., 27: 265–272, 1934.

[4] George H. Ashley, Penna. Topog. and Geol. Surv., Bull. G–1, 1931.

[5] The writers are indebted to Miss M. Grace Wilmarth, who has kindly checked the data on the early use of the term; letter of February 15, 1935.

[6] C. A. Ashburner, *Proc. Am. Phil. Soc.*, 16: 519–560, 1877.

[7] F. Platt and G. W. Platt, Penna. Second Geol. Surv., Vol. H2, 1877.

change our ideas about that locality. Evidently, in the case of Pocono, we are forced either to propose an entirely new term, or, and this is by far the more reasonable and least confusing course, accept a name, which, however dubious its origin, is made acceptable by long usage.

GEORGE H. ASHLEY
BRADFORD WILLARD

PENNSYLVANIA TOPOGRAPHIC AND GEOLOGIC SURVEY

DELAYED ACTION OF SELENIUM POISONING OF LIVE STOCK

THE various manifestations of selenium poisoning of live stock by ingesting grains, forages and native range plants carrying toxic and lethal quantities of selenium has received considerable attention during the past few years from chemists and physiologists in the U. S. Department of Agriculture and in a few state experiment stations. Through accumulative data covering many field and experimental cases, it appears that under certain conditions not understood at present an animal may not show any outward sign of poisoning perhaps for several months after grazing upon range plants carrying selenium. When the "break down" occurs, death usually follows in from one to six days. Those that survive seldom regain normalcy. Severe cases show much characteristic pathology.

It is indeed surprising to observe cattle and sheep in an apparently sound and healthy condition suddenly go "off feed," pass bloody urine and rapidly lose weight. To one not familiar with this type of poisoning, it is generally interpreted as due to some immediate physiological disturbance. As a matter of fact, it is now known that such cases may have grazed the causal toxicant months previous to the occurrence of the final acute stage.

O. A. BEATH

UNIVERSITY OF WYOMING

AQUATIC ANIMALS AS COLLECTORS

RECENTLY, when examining some young specimens of the Ocean Sunfish (*Orthagoriscus mola* and *Masturus lanceolatus*), these giants of the ocean, weighing from 400 to 2,000 pounds, I discovered certain young individuals, measuring 2½ inches, among the collections of fishes of the Museum of Comparative Zoology, Cambridge, Mass. They have been found in the stomach of a dolphin.

Another giant fresh-water fish is the Great Caspian Sturgeon (*Huso huso*), which also attains the weight of 2,000 pounds. The young of this species were unknown for a long time until I happened to discover them, as well as those of other sturgeons, in the stomachs of cat-fishes (*Silurus glanis*).

Thus, naturalists are indebted to the voracious dolphin in the ocean and to the voracious cat-fish in fresh waters for collecting the rarest specimens of the young of two giant fishes.

By publishing this short notice I would like to call the attention of my ichthyological colleagues to those facts and urge to lose no opportunity of dissecting the stomachs of voracious aquatic animals with a view to finding other fish which they have swallowed. Those creatures may prove of great assistance to us in collecting very rare specimens.

N. A. BORODIN

MUSEUM OF COMPARATIVE ZOOLOGY
CAMBRIDGE, MASS.

EXTENDED HIBERNATION IN THE TOAD

THE writer believes he has an example of extended hibernation in the common toad, *Bufo americanus*.[1] In 1908, the W. E. Caldwell Company, Louisville, Kentucky, constructed a structural steel plant over some filled swampy land. On November 1, 1934, twenty-six years later, while digging in one of the buildings for the placing of a new furnace, two toads were exhumed. The first was about four and one-half feet and the second nearly eight feet below the clay floor of the building. An examination of the walls of the pit showed the fill to be of yellow clay with an occasional small air space, none over one-half inch in diameter. There was no indication of any type of passage-way by which the toads may have entered. The closest distance from the pit to the wall of the building was twenty-five feet. The foundation of the building is fourteen inches thick and extends four and one-half feet below the clay floor of the building.

The workmen placed the first toad on the edge of the pit, believing it to be dead, but in a short time it hopped away. The second toad was saved. It was so thin that little remained but skin and bones. It revived to such an extent that it was able to hop and to turn over when placed on its back. When it was brought into the warm laboratory, it died within two hours.

P. A. DAVIES

UNIVERSITY OF LOUISVILLE

ECOLOGICAL NOTE

OUR *Felis domestica* recently committed a nuisance on a small rug. He then removed from the bookcase a Guidebook to Boston and a Guide to the Wild Flowers of Pennsylvania, with which he carefully covered his misdeed.

E. A. VUILLEUMIER

DICKINSON COLLEGE

[1] The writer is indebted to Mr. Walter E. Caldwell for calling his attention to the hibernation and for permission to examine the pit and to take the necessary measurements.

REPORTS

GRANTS FOR RESEARCH OF THE GEOLOGICAL SOCIETY OF AMERICA

THE following twenty-four grants have been approved recently by the Geological Society of America, in support of special research projects:

Robert T. Hill, Dallas, Texas, $1,200 to cover expenses connected with research in the history of geologic investigation in the Southwest.

F. M. Anderson, Berkeley, Calif., $300, to cover cost of illustrations connected with study of the stratigraphy and faunas of the Cretaceous deposits of northern and central California and Oregon.

Christina Lochman, Chicago, $1,000, to cover field, laboratory and office expenses for completion of memoir on the Upper Cambrian faunas of Montana, Wyoming and South Dakota.

R. S. Bassler, Washington, D. C., $600, for photographic assistance in preparation of paper on the stony bryozoa (Trepostomata).

Richard Foster Flint, New Haven, $475, to cover field and laboratory expenses connected with study of the Pleistocene drift borders across the Idaho-Washington line to the Cascade Mountains.

Charles A. Anderson, Berkeley, Calif., $350, for rock analyses for study of the volcanic history of the Clear Lake area north of San Francisco.

John T. Rouse, Clinton, N. Y., $425, for traveling and field expenses, study of the structure and tectonic history of the Absaroka volcanic area, Wyoming.

Charles H. Behre, Jr., Evanston, Ill., $1,000, to cover traveling, field and laboratory expenses connected with an examination of the geologic setting of the great depression of the South Park, Colorado.

Duncan Stewart, Jr., Northfield, Minn., $100, for thin sections in study of duplicate rock specimens from the Antarctic Archipelago and the South Orkney Islands.

James H. Gardner, Tulsa, Okla., and Donald C. Barton, Houston, Texas, $550, for expenses connected with the running of precision levels on salt domes in Texas and Louisiana, in order to determine possible differences in elevation caused by movement in the salt domes during coming years.

H. W. McGerrigle, Hanover, N. H., $500, for office expenses connected with study of the succession of faunas in the Philipsburg group of southern Quebec and northern Vermont.

H. R. Wanless, Urbana, Ill., $600, for field and miscellaneous expenses connected with determination of the correlation of coal seams and other strata of the Pennsylvanian between the eastern interior coal field and the Appalachian coal field.

F. M. Carpenter, Cambridge, Mass., $125, for expenses connected with the collecting of Permian fossil insects in Dickerson County, Kansas.

Julia Gardner, Washington, D. C., $700, for traveling and office expenses and assistance connected with study of the Tertiary faunas of northern Mexico and their relation to the faunas of the eastern Gulf Province. (This investigation was supported in 1933 and 1934).

Norman D. Newell, Lawrence, Kansas, $142, for traveling and field expenses for investigation of a fauna occurring in the Woodward formation in the Upper Cimarron Group.

Joseph A. Cushman, Sharon, Mass., $1,500, for clerical and other assistance in completion of monograph of the foraminiferal family *Nonionidae*.

Lewis B. Kellum, Ann Arbor, $2,000, to cover field expenses in connection with cooperative studies of the geologic history and structural development along the ancient continental margin in Coahuila and adjacent states. (This investigation was supported in 1933 and 1934).

Marcellus H. Stow, Lexington, Va., $288, for traveling and field expenses and photographic supplies, connected with investigation of the Paleocene and Eocene sedimentation and stratigraphy in the western part of the Bighorn Basin.

W. H. Twenhofel, Madison, Wis., and Frank F. Grout, Minneapolis, Minn., $1,000, for field and laboratory expenses of study of the accessory minerals in igneous rocks and pre-Cambrian sediments in the Lake Superior region. Half of this amount is to be expended by workers at the University of Minnesota and half by workers at the University of Wisconsin. (This investigation was supported in 1934).

Walter H. Bucher, Cincinnati, $800, to cover traveling and field expenses and assistance in connection with investigation of the Heart Mountain overthrust in Wyoming.

Henry S. Sharp, New York, $400, to cover traveling and field expenses connected with study of the origin, age, correlation and relationship to erosional surfaces in the adjacent plains, of the "Sub-summit" peneplain of the Beartooth Mountains.

Arthur D. Howard, New York, $344, to cover traveling and field expenses connected with study of the history of the Grand Canyon of the Yellowstone.

Frank J. Wright, Granville, Ohio, $475, for traveling and field expenses in connection with correlation of the erosion surfaces of the Bighorn Basin.

B. L. Miller and Maurice D. Ewing, Bethlehem, Pa., $2,000, for field expenses, equipment, assistance and supplies connected with seismic work on the eastern Continental Shelf.

One hundred and thirty-three research grants made by the Geological Society since December, 1932, amounted approximately to $125,000.

GRANTS FOR RESEARCH OF THE AMERICAN PHILOSOPHICAL SOCIETY

GRANTS to support special research projects by the American Philosophical Society from April, 1934, to March, 1935, were announced at the annual meeting. The value of the awards ranges from $50 to $6,000. Recipients of the grants and their projects are:

HELLMUT DE TERRA, Peabody Museum of Natural History, Yale University, to enable him to study the geological background of early man in Northern India through

the use of concerted methods of geology, paleontology and prehistory, and to search for early hominids and fossil anthropoid apes to advance our knowledge of man's evolution and his earliest cultures.

RALPH E. CLELAND, Goucher College, Baltimore, in support of his work for a cooperative cytogenetic and taxonomic attack upon the phylogeny and systematics of Oenothera (evening primrose), with special reference to the sub-genus onagra.

F. K. RICHTMYER, Cornell University, to enable him to continue his work on the determination of the widths, shapes and relative intensities of the lines in the x-ray spectra of the several elements; and the use of these data to compute the distribution of energy in the excited states of atoms.

FARRINGTON DANIELS and B. M. DUGGAR, University of Wisconsin, in support of a fundamental research in photosynthesis, concerned with a determination of the quantum efficiency in this process when employing monochromatic light in different regions of the spectrum using algae as test material.

K. LARK-HOROVITZ, Purdue University, in support of his investigation on the intensity of electron scattering by means of homeo-polar compounds.

HARRY SHULTZ VANDIVER, University of Texas, to enable him to continue his work on the computation and investigation of the properties of Bernoulli numbers with special application to Fermat's last theorem, perhaps the best known of all unsolved mathematical problems.

FRANK G. DUNNINGTON, California Institute of Technology, to enable him to continue his work on a precision determination of the specific charge of a free electron by a new deflection method.

N. T. BOBROVNIKOFF, of the Perkins Observatory, for investigations of stellar spectra, mostly in the red and infra-red, with a special attention to the band spectra.

JUDSON DALAND, Philadelphia Institute for Medical Research, in support of work on the biological effects of thymus extract (Hanson)—the accruing acceleration in the rate of growth and development in successive generations, from the extract of thymus.

FRANK C. JORDAN, for the Allegheny Observatory, to cover expenses in connection with the work on the measurement of plates and computations for the determination of stellar parallaxes.

C. E. MENDENHALL and G. BREIT, University of Wisconsin, in support of the experiments on nuclear disintegration and scattering with protons and deutons accelerated by about 300 K. V.

ALEXANDER PETRUNKEVITCH, Yale University, to enable him to continue his work on the physiology of digestion and digestive enzymes in spiders.

CHARLES E. ALLEN, University of Wisconsin, for the determination of the chromosome complements of heteroploid clones of sphaerocarpos.

HENRY A. PILSBRY, Academy of Natural Sciences, Philadelphia, to enable him to collect and make field studies of mollusks of Sonora and Sinaloa, Northwestern Mexico, with the object of determining the relation of the Sonoran fauna of our Southwest to the neotropical fauna of Mexico.

FRANCIS W. PENNELL, Academy of Natural Sciences, Philadelphia, to enable him to collect and make field studies of plants, especially of the family scrophulariacea, in Sonora and Sinaloa, Northwestern Mexico, considering the composition and distribution of the flora and its relation to that of the Southwestern United States and Southern Mexico.

EDGAR F. HOWARD, University Museum, University of Pennsylvania, to investigate the problem of man's antiquity in America, with particular reference to a study of possible routes of migrations from Asia.

FREDERICA DE LAGUNA, University Museum, University of Pennsylvania, to make an archeological investigation of the lower Yukon Valley from Koyukuk to Holy Cross.

CHARLES P. OLIVIER, Flower Observatory, University of Pennsylvania, for the study of meteor trains, including their heights, durations, drifts, spectra, constitution and other physical characteristics.

ALEXANDER BIDDLE, for the National Economy League, for (1) the state-wide gathering of facts on the 5,635 tax-levying units in Pennsylvania by the Pennsylvania Economic Council; (2) the study of Philadelphia government by the Philadelphia committee.

HARLAN T. STETSON, Harvard University, for investigation of cosmic terrestrial relations.

SPROUL OBSERVATORY, Swarthmore College, to determine the magnitude of stars utilizing the energy received from them in wave-lengths in the red and infra-red parts of the spectrum.

PERCY BUCHANAN, Naka Ku Nagoya, Japan, for the investigation of the early linguistic origins of Japanese.

CHARLES A. KOFOID, University of California, for a morphological and physiological investigation of the neuromotor system of the ciliate protozoa in all the major types of ciliates, with a view to defining the structure and function of such system.

REAR ADMIRAL JOHN D. NARES, for the International Hydrographic Bureau, Monte Carlo, for the preparation of base charts.

SCIENTIFIC APPARATUS AND LABORATORY METHODS

A SIMPLE PHOTOGRAPHIC RECORDING KYMOGRAPH[1]

WE wish to describe a photographic recording device which we have found so convenient and so satisfactory that we believe it may prove useful in other laboratories where kymographs are employed. Many tracings, ordinarily written on smoked drums, may advantageously be recorded with this apparatus, and the friction of lever points on paper and the laborious adjustment of these points to the writing surface may thereby be eliminated. Furthermore, this direct and practically undistorted recording of changes in the level of a liquid in a manometer provides an accurate

[1] Submitted for publication April 9, 1935.

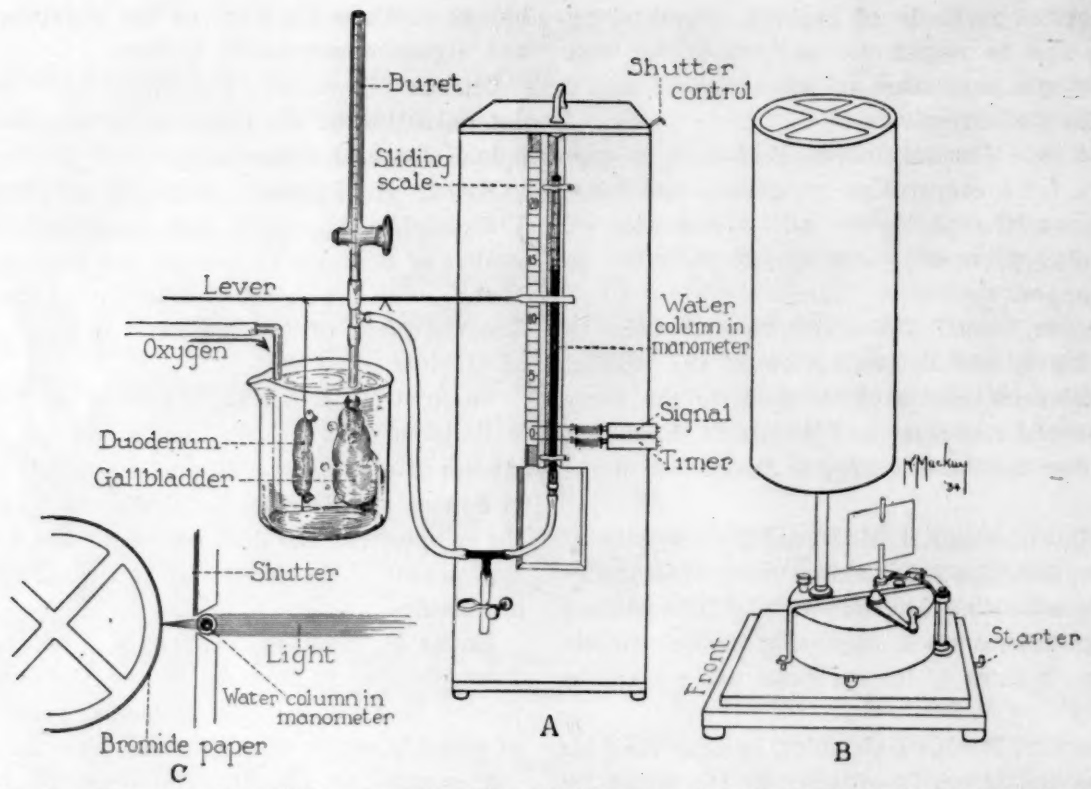

FIG. 1. The recording device in use. The significance of the initials is given in the text.

record of volume and pressure changes in any given system.

As early as 1883, E. A. Schäfer[2] utilized the photographic method to record changes in volume, whereas Baldes[3] and Corbeille, in 1929, utilized the method in recording plethysmograms.

Records were made on photographic bromide paper fastened to the drum of a "Harvard" kymograph (Fig. 1, B), which is enclosed in a light-tight box (Fig. 1, A). A vertical slit, 2 mm wide, opened or closed by means of a shutter, was made along the front elevation of this box and a water manometer was placed immediately in front of this slit. The source of light was an ordinary projection lamp, which was placed about 30 feet (9 m) from the recorder, so that the light rays were directed against the manometer. To secure optimal results it is essential that the effective light rays, the long axis of the manometer, the midline of the slit in the box and the axis of the revolving drum should be properly aligned (Fig. 1, C). The manometer, containing a liquid, functioned as a lens, so that light passing through the liquid was focused on the light-sensitive paper fixed to the revolving drum of the kymograph. It is apparent that changes in the level of the liquid were recorded on the paper by the marked contrast between the intensity of exposure above and below the level of the meniscus. Likewise, any movements of levers, time signals or markers may be recorded simultaneously with the changes in the level of the meniscus.

A manometer tube, of the type employed clinically for measuring spinal fluid pressures, was found convenient in our experiments. These tubes are of particular value for records of this sort, since they are accurately calibrated and the photograph of these lines on the record is of value in computing changes in the level of the meniscus. These tubes contain 0.02 cc of fluid per centimeter of length and thus permit the recording of changes in pressure without appreciable changes in the volume. A satisfactory type of contrast bromide paper, 70 feet (21.3 m) in length and either 6 or 12 inches (15.2 or 30.4 cm in width), is obtainable in rolls. A developer which gives the maximum of contrast must be used.

Reproductions of records made with the apparatus that has been described above accompany an article by Deissler and Higgins, entitled "The Extrahepatic Biliary Tract during Anaphylaxis"; this article has been accepted by *The American Journal of Physiology*.

KARL DEISSLER
GEORGE M. HIGGINS
CHARLES SHEARD

THE MAYO CLINIC AND
THE MAYO FOUNDATION,
ROCHESTER, MINNESOTA

A MICRO-METHOD FOR DETERMINING THE UTILIZATION OF CARBOHYDRATES AND POLYHYDRIC ALCOHOLS BY MICROORGANISMS

IT is sometimes desirable to know whether a single colony of bacteria, without further sub-culture, is composed of organisms capable of utilizing one or more particular carbohydrates. This can be easily and quickly accomplished by the following micro-technique.

[2] E. A. Schäfer, *Jour. Physiol.*, 5: 127–129, 1883–1884.
[3] E. J. Baldes and Catherine Corbeille, *Proc. Soc. Exper. Biol. and Med.*, 26: 711–715, May, 1929.

The colony is removed from the surface of the agar by a platinum inoculating loop and mixed with several loopfuls of a M/750 phosphate buffer at a pH of 7.3, containing 0.04 per cent. phenol red in a depression slide. By means of the loop (or a smaller one, if several substrates are to be studied) droplets are removed from the depression to the flat surface of the slide. A loopful of distilled water is mixed with one droplet as a control, and a loopful of a 1.0 per cent. distilled water solution of a given carbohydrate is mixed with another droplet. The suspensions of cells prepared in this manner are then taken up in capillary tubes having an inner diameter of 0.35 mm and observed for change in color of the indicator. If the substrate is oxidized the solution will become acid, due either to the liberation of fixed acid or to an excess CO_2 production, while the control will remain unchanged, since the CO_2 production is too low to affect the buffer. In the case of a 2 mm colony of *Escherichia coli* treated in this manner, the change from orange-red to yellow occurred within fifteen minutes, with glucose as substrate, while the control underwent no change over a period of several days in the incubator.

The same method has been fully tested on a slightly larger scale, using capillary tubes of 1 to 2 mm inner diameter, with the washed cells of luminous bacteria (*Vibrio phosphorescens* and *Achromobacter fischeri*) as well as *Escherichia coli* and yeast. Thirty substrates, including pentoses, hexoses, heptoses, polysaccharides and two-, three- and six-carbon polyhydric alcohols, have been tested with each of the above species. The method works equally well in small test-tubes, 10×75 mm, which insure partial anaerobiosis by virtue of the fact that oxygen diffuses in sufficiently rapidly only for the cells in the uppermost layer of the suspension to remain aerobic. Washing the cells with the aid of the centrifuge is desirable in order to get the results of the "resting" metabolism, uncomplicated and unobscured by extensive products and processes of vigorous growth. Except with the most slowly fermented substrates, such as dulcitol, the results are obtained within a few minutes, or at most a few hours. The rate depends, of course, on the concentration of cells, the concentration of buffer, and the rate and products of decomposition of the substrate, but in general, satisfactory results are obtained when washed cells from a heavily inoculated 18-hour nutrient agar Petri plate are resuspended in 15 to 20 cc of M/150 buffer. The suspension is aerated by a stream of air for about fifteen minutes, and 1 cc portions diluted with an equal volume of substrate solution in small test-tubes.

This method has given results entirely consistent with those found in the case of the aerobic oxidation of substrates by the "resting" cells of luminous bacteria in Warburg respirometers, except for glycerine, which is easily oxidized aerobically, but apparently not in a limited oxygen supply. While only the oxidations occurring at an initial pH of 7.3 have been studied, it should be possible, with appropriate indicators, to study different pH ranges.

Gas formation could be detected in the case of yeast, by large bubbles in the capillaries, but not very well with *Escherichia coli*. With the latter, gas formation could be detected by means of very small glass tubes, sealed at one end, and filled by a micro-pipette, and inverted in the small test-tube containing the suspension. In this case, however, gas was not formed from certain substrates apparently because acid accumulated so fast that the cells were precipitated in a few minutes. The accumulation of gas required incubation over night. No further change occurred after several days, and the controls never indicated any decided acid production or gave any indication of gas formation.

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SPECIAL ARTICLES

THE CULTURE OF WHOLE ORGANS

THE method to be described consists of the transplantation of an organ or of any part of the body into a sterile chamber, and of its artificial feeding with a nutrient fluid through the arteries. It is not in any way a substitute for the method of tissue culture. Its techniques, as well as its purposes, are quite different. As is well known, tissues and blood cells grow like bacteria in flasks containing appropriate media. The techniques for the cultivation of tissues are somewhat analogous to bacteriological techniques, although far more delicate. But it is through the employment of complex mechanical and surgical procedures that organs are enabled to live isolated from the body. Tissue culture deals with cells as units of bodily structures; the new method, with cellular societies as organic wholes. Its ultimate purposes are the manufacture *in vitro* of the secretions of endocrine glands, the isolation of the substances essential to the growth, differentiation and functional activity of those glands, the discovery of the laws of the association of organs, the production *in vitro* and the treatment of organic and arterial diseases, etc.

The idea of maintaining alive a portion of the body in order to study its functions is not new. In 1812, the physiologist Le Gallois[1] wrote that, "if one could sub-

stitute for the heart a kind of injection . . . of arterial blood, either natural or artificially made, . . . one would succeed easily in maintaining alive indefinitely any part of the body whatsoever." But Le Gallois did not attempt to supply organs with such artificial circulation. The first perfusion apparatus probably originated from Ludwig's laboratory. In 1866, de Cyon kept the heart of a frog beating for 48 hours.[2] Later, he demonstrated by a similar technique that a perfused liver still manufactures urea. Brown-Séquard observed the reestablishment of certain cerebral functions by circulating blood through the vessels of a head separated from its body.[3] The later history of the perfusion of organs is well known.[4] But the best and more recently constructed apparatus have never been capable of maintaining a gland in a condition of survival for more than a few hours. Even during this short time the organ was being rapidly invaded by bacteria. It is only recently that surgical and mechanical procedures became sufficiently perfected to allow organs to be cultivated *in vitro*. With the study of the transplantation of organs and their blood vessels,[5] techniques were developed for handling the arteries, washing the organ free from blood without injuring the cells, and preventing emboli. During the last war, antiseptic procedures that permit complete protection of tissues from bacteria in the course of surgical operations came into being in the laboratories supported by the Rockefeller Institute in Compiègne. But there was no apparatus capable of playing the rôle of heart and lungs and of keeping an organ free from infection indefinitely. In this laboratory, a long search has been made for the proper apparatus. An ingenious magnetic pump was constructed some years ago.[6] Later, a much simpler apparatus was designed,[7] which maintained an artificial circulation through a segment of artery for a month without infection. Still other kinds of apparatus, based on different principles, were built in the following years. Finally, in 1935, a model was developed that has for the first time permitted an entire organ to live outside of the body.[8] The purpose of the present article is merely to show how, after 123 years, the conception of Le Gallois has been realized.

The organs are removed from an animal that has just been killed by bleeding under anesthesia. Adult fowls or cats are generally used. An ovary, a suprarenal, or a thyroid gland is removed by a procedure similar to that employed in the transplantation in mass of organs.[9] That is, the organ is extirpated, together with its surrounding tissues, arteries, veins, nerves and lymph vessels. In the explantation of the ovary, for instance, the Fallopian tube, the ovary and a flap of peritoneum and connective tissue containing the ovarian artery are dissected as far as the aorta and removed. During the course of the operation, the abdominal cavity and the organ are constantly protected with gauze pads soaked in Dakin solution. In this manner, the operation can be performed successfully in a room that is not dust-proof.

The culture medium varies in quantity and composition. In order that the supply of glucose and bicarbonate may be sufficient for several days, the volume of medium must be about 2,000 times greater than that of the tissues. For instance, a cat's thyroid gland, varying in weight from 85 to 110 mgs, demands about 230 cc of nutrient fluid. The apparatus may be operated with from 200 to 900 cc of medium. This medium consists of blood serum or of more or less growth-activating solutions prepared by L. E. Baker. Such solutions contain protein split-products, hemin, cysteine, insulin, thyroxine, glutathione, vitamin A, ascorbic acid, blood serum, etc. A small amount of phenol red is indispensable as an indicator of the metabolic activity of the organ, as well as of the occurrence of bacterial infection. In some experiments, hemoglobin is added to the fluid. The gaseous medium consists of 40 per cent. oxygen, and from 3 to 4 per cent. carbon dioxide, the remaining part being nitrogen.

The organ is introduced into the culture chamber while being protected by a sheet of Cellophane, and the artery is connected with the cannula of the apparatus. Then the chamber is closed by a rubber stopper and sealed with a cellulose acetate cement. The apparatus maintains a sterile pulsating circulation through the organ for a length of time limited only by the condition of the organ and the perfusion fluid. The pulsation rate and both maximum and minimum pulsation pressures are adjustable. The perfusion fluid is kept well aerated and in contact with gas of controlled composition. Pulsation pressures are practically unaffected by changes in the rate of flow through the organ. Filming and evaporation are prevented. Both the organ and perfusion fluid may be observed at all times. The apparatus is kept in an incubator at a temperature of 37–38° C. The circulation is started about 1 hour after the death of the animal. The number of pulsations, in most of the experiments, has been about 60 per minute, the systolic pressure, 120

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1 C. J. J. Le Gallois, "Expériences sur le principe de la vie," Paris, 1812.

2 E. De Cyon, *Arch. ges. Physiol.* (Pflüger's), 77: 215, 1899; *Compt. rend. Soc. Biol.*, 52: 372, 1900.

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4 A. E. Belt, H. P. Smith and G. H. Whipple, *Am. Jour. Physiol.*, 52: 101, 1920.

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9 A. Carrel, *loc. cit.*

mm Hg., and the diastolic pressure, 60 mm Hg. Some fluid may leak and spurt from small blood vessels without markedly lowering the pressure. The progressive decrease of the pH of the medium is detected by comparing the color of the fluid feed tube of the apparatus with that of a set of standard tubes.

Twenty-six experiments have been performed since the last model of the apparatus was made. The organs were thyroid, ovary, suprarenal, spleen, heart and kidney. Some organs were transferred several times from apparatus to apparatus. Infection occurred twice only. This accident took place in spleens that obviously were contaminated before removal from the abdomen. Thyroid glands were kept more than 20 days with pulsating arteries and active circulation. They could have remained in the apparatus much longer. No emboli and no important hemorrhages were observed. The lowering of the pH of the medium occurred more or less rapidly according to its composition. In diluted blood serum, cat's thyroid glands consumed only about 7 mg of glucose per 24 hours. When they were perfused with a growth-promoting fluid, the glucose consumption increased more than three times.

Changes in form and volume took place in the organs from day to day. Thyroid glands perfused with diluted serum were observed to decrease in size progressively. On the contrary, ovaries or thyroids perfused with a growth-promoting medium modified their form and grew rapidly. In 5 days, the weight of an ovary increased from about 90 to 284 mg. Simultaneously, three corpora lutea developed. At the end of the experiments, that is, after from 5 to 21 days, small fragments taken from the organs and cultivated in flasks engendered active colonies of epithelial cells and fibroblasts. The epithelium of an adult thyroid was found to have recuperated its fetal activity after being perfused for a few days with a growth-activating fluid. The sections showed an almost normal structure of fragments of the thyroid, even when the gland had been roughly treated and perfused with dilute serum for a long period of time, when the pH had been lowered to 7.2 for several days or when the circulation had markedly decreased. The presence of colloid was observed in some follicles. If perfused with a growth-promoting fluid, the structure of the gland was altered. The colloid substance disappeared. The epithelial cells proliferated within and also outside the follicles. In ovaries treated in the same manner, growth was also accompanied by disorganization. There was a luxuriant and disordered proliferation of the stroma and of the epithelial cells. Obviously, a large amount of new tissue had been manufactured by the organ. The fluids that had circulated through the apparatus were tested for modifications induced by the organs. In every case, the thyroid glands were found to have set free substances that stimulated the proliferation of leucocytes more or less markedly.

The structural and functional changes undergone by the organs during their life *in vitro* are complex. They obviously depend on the chemical composition and the physicochemical and physical conditions of the perfusing fluid. They will be discussed in subsequent articles. From the present experiments, it must merely be concluded that an entire organ, such as an ovary, has been maintained alive *in vitro*. It not only survived, but increased in size and in weight. This increase was due to the appearance of new cells and tissues. It is, therefore, probable that this method provides important uses in physiological chemistry, physiology and pathology.

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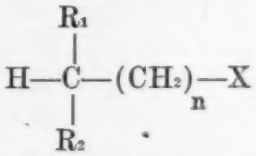
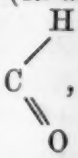
ANALYSIS OF ROTATORY DISPERSION OF CHEMICALLY ANALOGOUS SUBSTANCES

IN view of an article by W. Kuhn and H. Biller announced to appear in *Z. phys. Chem.*, "Drehungsbeitrag chromophorer Gruppen bei analog gebauten Verbindungen," we wish to report briefly the results of similar work which has been in progress in our laboratory in course of several years.

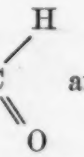
In Table I are given the directions of the partial rotations of the individual absorption regions in substances of the general type of



(R_1 and R_2 being alkyl groups, X a functional group,



, N_3, SH, Halogen; n = 0 or an integer). All substances in which X = N_3, NH_2 and



are configurationally correlated; when X = SH or Halogen, all substances in which n = an integer are likewise configurationally correlated by direct chemical methods and those in which n = 0 are not so correlated.

The most significant facts appearing from the data given in Table I are:

(1) The band of group X with the lowest frequency in some instances furnishes the principal partial rotation determining the direction of the optical rotation of the substance in the visible.

In other substances the partial contribution of the absorption region of low frequency depends upon the

TABLE I

	Compounds	Rotation in the visible	First absorption band in A.	Contribution of first band.	Second absorption region	Contribution of second absorption region	Sum of all other contributions
	Aldehydes						
	2-methylbutanal-1	−	2960	−			?
I.	3-methylpentanal-1	+	2940	+			−
	4-methylhexanal-1	−	2940	+			−
	Azides						
	2-azidooctane	+	2880	inactive	from 2200	+	?
II.	1-azido-2-methylbutane	−	2880	"	"	−	+
	1-azido-2-methylnonane	+	2880	"	"	−	+
	1-azido-3-methylpentane	−	2880	"	"	−	+
	Amino—						
	2-aminooctane	+	≦ 2300	−			+
III.	2-aminooctane hydrochloride	−	≦ 2100	−			
	1-amino-2-methylbutane	+	≦ 2300	+			−
	Thio—						
	2-thiobutane	−	2300	inactive	from 2100	−	?
IV.	2-thioheptane	−	2300	"	"	−	?
	1-thio-2-methylbutane	−	2300	"	"	+	−
	*Iodo—						
	2-iodobutane	+	2630	+	from 2000	+	?
	2-iodooctane	+	2630	+	"	+	?
	1-iodo-2-methylbutane	−	2570	?	"	+	−
V.	1-iodo-2-methylheptane	−	2570	?	"	+	−
	1-iodo-2-methylnonane	−	2570	?	"	+	−
	1-iodo-3-methylhexane	−	2570	−	"	−	?
	1-iodo-4-methylheptane	−	2570	−	"	−	?
	1-bromo-2-methylbutane	−	2000	+		−	
	Isopropyl Derivatives						
	2-iodo-3-methylbutane	+	2670	+	from 2000	−	
	4-iodo-5-methylhexane	−	2670	negligible	"	−	
VI.	1-iodo-2, 3-dimethylbutane	−	2570	"	"	−	
	1-iodo-3, 4-dimethylpentane	−	2570	− (slightly)	"	−	
	1-azido-2, 3-dimethylbutane	−	2880	inactive	from 2200	−	+

* Most of the normal halides were prepared by Mr. R. E. Marker.
The detailed results on these substances will be published under joint authorship.

values of n, and in one case depends upon the value of R_1.

(2) In those groups of substances in which all members are configurationally correlated (I, II, III) the direction of the predominating partial rotation of X changes sign when n passes from the value 0 to that of an integer.

The case of the halides of the normal series needs special discussion. In the secondary halides, both the first and the second absorption regions of the halogen atom seem to be active and to furnish the major part of the rotation in the visible region. In the iodides having n = 1, the principal contribution in the visible apparently is furnished by the third absorption region of the iodine atom, the first and second being of opposite sign and of small numerical value. In the bromide the rotation in the visible seems to be furnished principally by the second absorption region of the bromine atom, the first being of opposite sign and of small value.

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